liver damage or gastrointestinal bleeding). OTC drug products containing internal analgesic/antipyretic active ingredients may cause similar adverse effects. FDA concludes that the labeling of OTC drug products containing internal analgesic/antipyretic active ingredients should advise consumers with a history of heavy alcohol use to consult a physician. Accordingly, any OTC drug product, labeled for adult use, containing any internal analgesic/antipyretic active ingredients (including, but not limited to, acetaminophen, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate) alone or in combination shall bear an alcohol warning statement in its labeling as follows:

(1) *Acetaminophen.* ''Alcohol Warning'' [heading in boldface type]: ''If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.''

(2) *Nonsteroidal anti-inflammatory analgesic/antipyretic active ingredients—including but not limited to aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate.* ''Alcohol Warning'' [heading in boldface type]: ''If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take [insert one nonsteroidal anti-inflammatory analgesic/antipyretic active ingredient] or other pain relievers/fever reducers. [Insert one nonsteroidal anti-inflammatory analgesic/antipyretic active ingredient] may cause stomach bleeding.''

(3) *Combinations of acetaminophen with nonsteroidal anti-inflammatory analgesic/antipyretic active ingredients—including but not limited to aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate.* ''Alcohol Warning'' [heading in boldface type]: ''If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take [insert acetaminophen and one nonsteroidal anti-inflammatory analgesic/antipyretic active ingredient—including, but not limited to aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate] or other pain relievers/fever reducers. [Acetaminophen and (insert one nonsteroidal anti-inflammatory analgesic/antipyretic ingredient—including, but not limited to aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate] may cause liver damage and stomach bleeding.''

(b) *Requirements to supplement approved application.* Holders of approved applications for OTC drug products that contain internal analgesic/antipyretic active ingredients that are subject to the requirements of paragraph (a) of this section must submit supplements under § 314.70(c) of this chapter to include the required warning in the product's labeling. Such labeling may be put into use without advance approval of FDA provided it includes the exact information included in paragraph (a) of this section.

(c) Any drug product subject to this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after April 23, 1999, is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) and is subject to regulatory action.

[63 FR 56801, Oct. 23, 1998]

§ 201.323 Aluminum in large and small volume parenterals used in total parenteral nutrition.

(a) The aluminum content of large volume parenteral (LVP) drug products used in total parenteral nutrition (TPN) therapy must not exceed 25 micrograms per liter (µg/L).

(b) The package insert of LVP's used in TPN therapy must state that the drug product contains no more than 25 µg/L of aluminum. This information must be contained in the ''Precautions'' section of the labeling of all large volume parenterals used in TPN therapy.

(c) Except as provided in paragraph (d) of this section, the maximum level of aluminum present at expiry must be stated on the immediate container label of all small volume parenteral (SVP) drug products and pharmacy

bulk packages (PBPs) used in the preparation of TPN solutions. The aluminum content must be stated as follows: ''Contains no more than ___ µg/L of aluminum.'' The immediate container label of all SVP's and PBP's that are lyophilized powders used in the preparation of TPN solutions must contain the following statement: ''When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than ___ µg/L.'' This maximum level of aluminum must be stated as the highest of:

(1) The highest level for the batches produced during the last 3 years;

(2) The highest level for the latest five batches, or

(3) The maximum historical level, but only until completion of production of the first five batches after July 26, 2004.

(d) If the maximum level of aluminum is 25 µg/L or less, instead of stating the exact amount of aluminum as required in paragraph (c) of this section, the immediate container label may state: ''Contains no more than 25 µg/L of aluminum.'' If the SVP or PBP is a lyophilized powder, the immediate container label may state: ''When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L''.

(e) The package insert for all LVP's, all SVP's, and PBP's used in TPN must contain a warning statement. This warning must be contained in the ''Warnings'' section of the labeling. The warning must state:

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

(f) Applicants and manufacturers must use validated assay methods to determine the aluminum content in parenteral drug products. The assay methods must comply with current good manufacturing practice requirements. Applicants must submit to the Food and Drug Administration validation of the method used and release data for several batches. Manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections. Holders of pending applications must submit an amendment under §314.60 or §314.96 of this chapter.

[65 FR 4110, Jan. 26, 2000, as amended at 67 FR 70691, Nov. 26, 2002; 68 FR 32981, June 3, 2003]

APPENDIX A TO PART 201—EXAMPLES OF GRAPHIC ENHANCEMENTS USED BY FDA

I. SECTION 201.66 STANDARD LABELING FORMAT

A. Overall

1. The ''Drug Facts'' labeling is set off in a box or similar enclosure by the use of a barline with all black type printed on a white, color contrasting background.

B. Typeface and size

1. ''Drug Facts'' is set in 14 point Helvetica Bold Italic, left justified.

2. ''Drug Facts (continued)'' is set in 8 point Helvetica Bold Italic for the words ''Drug Facts'' and 8 point Helvetica Regular for the word ''(continued)'' and is left justified.

3. The headings (e.g., ''Directions'') are set in 8 point Helvetica Bold Italic, left justified.

4. The subheadings (e.g., ''Ask a doctor or pharmacist before use if you are'') are set in 6 point Helvetica Bold, left justified.

5. The information is set in 6 point Helvetica Regular with 6.5 point leading, left justified.

6. The heading ''Purpose'' is right justified.

7. The bullet is a 5-point solid square.

8. Two em spacing separates bullets when more than one bullet is on the same line.

9. A table format is used for 3 or more dosage directions.

10. A graphic appears at the bottom of the first panel leading the reader to the next panel.

C. Barlines and hairlines

1. A 2.5-point horizontal barline extends to each end of the ''Drug Facts'' box (or similar enclosure), providing separation between each of the headings.

2. A 0.5-point horizontal hairline extends within 2 spaces on either side of the ''Drug Facts'' box (or similar enclosure), immediately following the title and immediately preceding the subheadings.

3. A 0.5-point horizontal hairline follows the title, immediately preceding the heading, when a heading appears on a subsequent panel immediately after the ''Drug Facts (continued)'' title.

D. Box or Enclosure

1. All information is enclosed by a 2.5-point barline.

II. SECTION 201.66 MODIFIED LABELING FORMAT

A. Overall

1. The ''Drug Facts'' labeling is presented in all black type printed on a white color contrasting background.

B. Typeface and size

1. ''Drug Facts'' is set in 9 point Helvetica Bold Italic, left justified.

2. The headings (e.g., ''Directions'') are set in 8 point Helvetica Bold Italic, left justified.

3. The subheadings (e.g., ''Ask a doctor or pharmacist before use if you are'') are set in 6 point Helvetica Bold, left justified.

4. The information is set in 6 point Helvetica Regular with 6.5 point leading, left justified.

5. The heading ''Purpose'' is right justified.

6. The bullet is a 5-point solid square.

7. Bulleted information may start on same line as headings (except for the ''Warnings'' heading) and subheadings, with 2 em spacing separating bullets, and need not be vertically aligned.

C. Barlines and hairlines

1. A 2.5-point horizontal barline extends to each end of the ''Drug Facts'' box (or similar enclosure), providing separation between each of the headings.

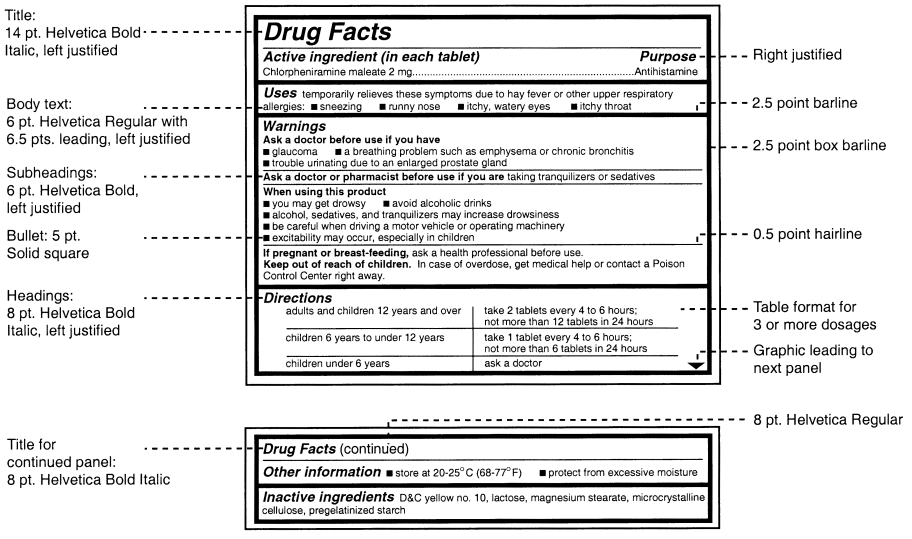
2. A 0.5-point horizontal hairline extends within 2 spaces on either side of the ''Drug Facts'' box (or similar enclosure), immediately following the title and immediately preceding the subheadings.

D. Box or Enclosure

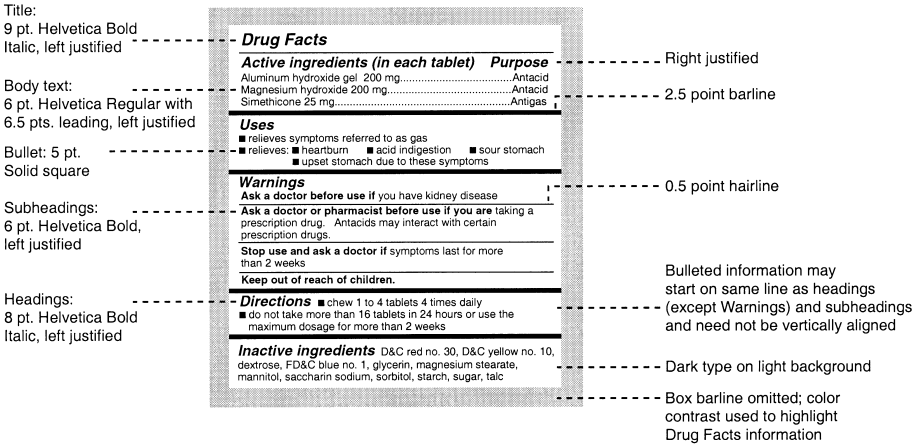
1. All information is set off by color contrast. No barline is used.

III. EXAMPLES OF §201.66 STANDARD LABELING AND MODIFIED LABELING FORMATS

A. SECTION 201.66 STANDARD LABELING FORMAT



B. SECTION 201.66 MODIFIED LABELING FORMAT



PART 202—PRESCRIPTION DRUG ADVERTISING

AUTHORITY: 21 U.S.C. 321, 331, 352, 355, 360b, 371.

§ 202.1 Prescription-drug advertisements.

(a)(1) The ingredient information required by section 502(n) of the Federal Food, Drug, and Cosmetic Act shall appear together, without any intervening written, printed, or graphic matter, except the proprietary names of ingredients, which may be included with the listing of established names.

(2) The order of listing of ingredients in the advertisement shall be the same as the order of listing of ingredients on the label of the product, and the information presented in the advertisement concerning the quantity of each such ingredient shall be the same as the corresponding information on the label of the product.

(3) The advertisement shall not employ a fanciful proprietary name for the drug or any ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness or composition, when, in fact, the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name.

(4) The advertisement shall not feature inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation.

(5) The advertisement shall not designate a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.

(b)(1) If an advertisement for a prescription drug bears a proprietary name or designation for the drug or any ingredient thereof, the established name, if such there be, corresponding to such proprietary name or designation shall accompany such proprietary name or designation each time it is featured in the advertisement for the drug; but, except as provided below in this subparagraph, the established name need not be used with the proprietary name or designation in the running text of the advertisement. On any page of an advertisement in which the proprietary name or designation is not featured but is used in the running text, the established name shall be used at least once in the running text in association with such proprietary name or designation and in the same type size used in the running text: *Provided, however,* That if the proprietary